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Meldonium use by athletes at the Baku 2015 European Games

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ABSTRACT

Background The aim of this report was to estimate the prevalence of meldonium use in athletes competing in the Baku 2015 European Games to contribute to the surveillance of substances on the 2015 World Anti-Doping Agency (WADA) Monitoring Program. Meldonium is reported to be used by athletes to potentially enhance personal performance and shorten the recovery period after physical activity.

Methods Three sources of data were reviewed to determine the prevalence of meldonium use during the Games including: (1) athlete self-reported declarations of drug and supplement use; (2) declarations from National Olympic Committee medical teams of the list of medicines that they imported into Azerbaijan as part of their stock of drugs for administration; (3) results from the antidoping laboratories reporting the detection of meldonium.

Results Meldonium was declared as imported into Azerbaijan by 2 of 50 National Olympic Committee medical teams at the Games, but athletes from 6 countries declared the use of meldonium. Only 23 of the 662 (3.5%) athletes tested from 8 to 28 June 2015 declared the personal use of meldonium, which included 13 competition winners. However, 66 of the total 762 (8.7%) athlete urine samples analysed during the Games and during precompetition tested positive for meldonium. Meldonium use was detected in athletes competing in 15 of the 21 sports during the Games.

Conclusions This study highlights the widespread and inappropriate use and prescribing of this prescription drug in a generally healthy athlete population. Subsequent to these findings, WADA has included meldonium as a prohibited substance on the 2016 List of Prohibited Substances.

INTRODUCTION

The aim of this report is to identify the prevalence of meldonium use in the 5632 athletes competing in the Baku 2015 European Games held in Azerbaijan from 12 to 28 June 2015, with the purpose of contributing to the surveillance of substances listed on the 2015 World Anti-Doping Agency (WADA) Monitoring Program.

Clinical use of meldonium

Meldonium is registered and prescribed as a drug for human therapeutic use in Latvia, Russia, Ukraine, Georgia, Kazakhstan, Azerbaijan, Belarus, Uzbekistan, Moldova and Kyrgyzstan, and is manufactured under a number of brand names. These include: Cardionate; Idrinol; Medatern; Melfor; Midolat; Mildronate; Mildroxyn and Vazomag in Russia; and Metamax; Methyldronat; Metonat;

Mildronate; Trizipin; Vazonat and Vazopro in Ukraine.¹

Meldonium—chemical name: 3-(2,2,2-Trimethyldiazaniumyl) propanoate—is an inhibitor of carnitine synthesis and is reported to have cardioprotective and anti-ischaemic effects. It has been used in a variety of disorders including for the management of ischaemic heart disease and ischaemic cerebrovascular disturbances. Typical therapeutic oral and intravenous doses range from 500 mg to 1 g of meldonium daily. A course of 500 mg given four times daily for 7–10 days has been reported to be used clinically in alcohol abstinence syndrome.¹

The WADA publishes the List of Prohibited Substances and Methods at least annually. This list includes any substance or method that has medical or scientific evidence, whether alone or in combination, to enhance performance, to represent health risk to the athlete or to violate the spirit of sport.²

In addition, WADA also publishes a list of substances on the WADA Monitoring Program, which is composed of substances that are under surveillance by WADA to detect possible patterns of use or misuse in sport. The substances specifically being monitored by WADA during 2015 were:

- ▶ Stimulants including: bupropion, caffeine, nicotine, phenylephrine, phenylpropanolamine, pipradrol and synephrine;
- ▶ Narcotics including: hydrocodone, mitragynine, morphine/codeine ratio, tapentadol and tramadol;
- ▶ Glucocorticoids;
- ▶ Telmisartan;
- ▶ Meldonium.

WADA accredited laboratories responsible for testing urine or blood samples from athletes are requested to test and report on such substances being monitored. This information is used by WADA as evidence to inform future decisions about whether to prohibit specific substances or not. It should be noted that the reported presence of a drug on the WADA Monitoring Program in an athlete's blood or urine sample would not result in an antidoping rule violation by the athlete.

Meldonium was added to the WADA Monitoring Program in January 2015 in light of anecdotal reports of use among the athlete population during the London 2012 Olympic and Paralympic Games. During London 2012, declarations from each team were required for all medicines being imported into the UK. Five teams declared the importation and possession of meldonium for legitimate use by their own medical teams accompanying the athletes.



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METHODS

Three sources of data were reviewed by the EOC Medical and Anti-Doping Commission to determine the prevalence of meldonium use during the Baku 2015 European Games.

Self-reported meldonium use on doping control forms

At the time of providing a urine or blood sample at a doping control station, all athletes were asked to declare any medications or nutritional supplements taken during the previous 7 days. Athletes were also asked to sign to indicate that the samples could be used anonymously for antidoping research purposes.

Members of the European Olympic Committees (EOC) Medical and Anti-Doping Commission present in Baku during the Games undertook a review of the doping control forms and recorded the self-reported declarations made by the athletes.

Declaration of meldonium as medical team stock

Each country's National Olympic Committee (NOC) participating in the Games was required to submit a declaration to the Baku 2015 Games Medical Services of all medicine supplies being imported into Azerbaijan for use by their own medical teams during the time of the Games. These declarations were reviewed for self-reported meldonium stock, which the teams were carrying for the purpose of administration to members of their team.

Laboratory detection of meldonium in doping control samples

Two WADA accredited laboratories were used to analyse urine and blood samples during the Games. These were located in Moscow, Russia, and in Seibersdorf, Austria. Sample testing was split between the two laboratories, based on a preplanned agreement related to specific sports.

Both WADA accredited laboratories screened all urine samples specifically for the presence of meldonium. These data were provided directly to WADA as part of the Monitoring Program surveillance.

RESULTS

Self-declaration of meldonium

There were a total of 864 tests, which included 762 urine and 102 blood tests from 46 of the 50 participating NOCs, undertaken by the Baku 2015 Anti-Doping Services. Of these, 662 (297 female/365 male) were undertaken from 8 to 28 June 2015, and the rest were undertaken as pregames testing in the month prior to the Games.

Of all Baku 2015 Doping Control Forms reviewed from 8 to 28 June 2015, 525 of 662 (80%) had a self-reported declaration by the athlete for either a medication or nutritional supplement.

A total of 23 of the 662 (3.5%) athletes tested from 8 to 28 June declared the personal use of meldonium at the time of the Games.

There were 13 competition winners who declared taking meldonium:

- ▶ Six of these athletes won either a gold medal or first place in the competition;
- ▶ Five of these athletes won a silver medal or came second place;
- ▶ Two of these athletes won a bronze medal or came third place.

Athletes declaring meldonium use were competing in one of the following sports: taekwondo, wrestling, diving, swimming,

road cycling, athletics (long distance running and high jump), fencing, boxing, gymnastics, volleyball and canoe-sprint.

Laboratory detection of meldonium

A summary of findings from both, the Moscow and Seibersdorf laboratories, relating to substances on the 2015 WADA Monitoring Program are provided below. Only the data for meldonium are discussed in this report.

Combined laboratory data

- ▶ Of 762 urine samples analysed, 66 cases of meldonium were reported (8.7%).
- ▶ Both laboratories reported meldonium >100 ng/mL; the Moscow laboratory provided estimated concentrations in the range of 0.7–273 µg/mL; estimated concentrations were not available for the Seibersdorf laboratory.

Moscow laboratory data

Four hundred and fifty urine samples were analysed and 48 meldonium cases reported.

Seibersdorf laboratory data

Three hundred and twelve urine samples were tested and 18 meldonium cases reported.

Comparison of self-reported versus laboratory-detected meldonium

The table below presents the comparison of self-reported declared use by athletes versus the laboratory detection in individual samples by sport ([table 1](#)).

Importation of medicines by NOC teams

Of the 50 NOCs represented at the Games, the importation of meldonium into Azerbaijan was declared to the Games Medical Services by 2 NOCs as stock for potential issue or administration by their team doctors.

- ▶ One country declared: 20 ampoules of meldonium 500 mg solution for injection
 - ▶ One country declared: 120 tablets of meldonium 250 mg
- However, athletes from six different countries declared the use of the drug on the doping control forms. There are three possible reasons for this:

1. The athletes had personal supplies of meldonium, which was not required to be declared at the time of importation;
2. The NOC medical staff members were unaware that one or more of their athletes were taking meldonium;
3. The NOC failed to declare this drug as being imported.

DISCUSSION

Estimate of prevalence of meldonium use

Meldonium use was detected across athletes competing in 15 of the 21 (71.4%) sports staged during the Games. The sample of 662 athletes tested represented a cross-selection of athletes from 46 of the 50 (92%) NOC's participating.

There was significant under-reporting of the use of this drug by athletes in most sports. Only 23 (3.0%) of the 662 athletes tested self-reported taking the drug, compared to 66 (8.7%) athletes who actually tested positive for meldonium. Of the 66 (65%) athletes who tested positive for meldonium, 43 did not declare taking the drug in the past 7 days. This clearly indicates significantly more widespread use of this drug than was openly declared by athletes at the Games.

Owing to the blinding of personal and demographic details prior to sending the samples to the laboratories, it is not known

Table 1 Laboratory meldonium findings versus athlete declared use

	Number of urine samples (includes precompetition testing)	Meldonium >100ng/mL	Percentage of samples positive for meldonium	Use declared by athlete (from 8 to 28 June 2015 only)	Percentage declared by athlete (from 8 to 28 June 2015 only)
Aquatics	137	9	6.6	2	1.5
Archery	11	1	9	0	0
Athletics	40	3	7.5	2	5
Badminton	11	0	0	0	0
Basketball	11	1	9	0	0
Boxing	53	2	3.8	1	1.5
Canoe/Kayak	48	15	31.3	2	4
Cycling	90	2	2.2	1	0.8
Fencing	24	0	0	2	8
Football	4	0	0	0	0
Gymnastics	26	7	26.9	1	3.8
Judo	53	0	0	0	0
Karate	28	1	3.6	0	0
Sambo	9	3	33.3	0	0
Shooting	45	0	0	0	0
Sport Climbing	4	2	50	0	0
Table Tennis	14	0	0	0	0
Taekwondo	36	5	13.9	6	16.7
Triathlon	33	1	3	0	0
Volleyball	21	3	14.3	2	9.5
Wrestling	64	11	17.2	4	4.5
Total	762	66	8.7 (of total number of urine tests)	23	3.0 (of athletes tested between 8 and 28 June 2015)

which specific countries the athletes who tested positive for meldonium came from. Thus direct extrapolation of this 8.7% prevalence to the wider European Games athlete population may not necessarily indicate the extent of use on a country-by-country basis.

The availability and accessibility of the drug to athletes across Europe is an important consideration in assessing the actual spread of meldonium use in athletes across Europe. In addition, the recognised medical use and prescription of meldonium in a number of countries will also potentially impact on the number of positive findings reported by the laboratories for athletes from those countries.

Meldonium is reported to be registered for medical use in seven Eastern European countries that competed at the Baku 2015 Games, including Latvia, Russia, Ukraine, Georgia, Azerbaijan, Belarus and Moldova. The number of athletes from these countries represented a total of 23.2% (1306 of 5632) of the entire athlete population competing at the Games.

The geographical commercial availability of meldonium for medical use correlates with the countries of origin of the athletes who self-declared its use, and also correlates with the NOC medical teams who carried it as team stock. The self-reported declarations of meldonium in the doping control forms suggests that it is likely that there is higher prevalence of use in countries where meldonium is registered and prescribed compared to countries where meldonium is not registered for medical use.

However, it is likely that athletes and healthcare providers from any country where the drug is not officially registered for medical use could easily obtain the drug through medicine importation and exportation routes, and even more easily through online purchases. There are numerous Internet sites advertising meldonium for postal purchase to any country worldwide.

Not all athletes were tested during the games, and so actual prevalence cannot be accurately determined. However, extrapolation of the 8.7% prevalence of meldonium to the athletes from the seven competing countries where meldonium is registered for medical use would equate to a total of 114 athletes. Extrapolation to the entire general athlete population would be 490 athletes, but this is likely to be an overestimate. The estimated number of athletes taking meldonium during the 2015 Games is likely to lie somewhere within this range.

The significant under-declaration of meldonium use by athletes raises suspicion that many athletes did not want to let the antidoping authorities know about their use of meldonium. The doping control form, which the athletes completed at the time of sample collection at the Baku Games, specifically asked the individual athlete to 'list all medications and nutritional supplements taken during the past seven days'; all of the athletes then signed a declaration on the form stating that the information they have given on the document is correct.

This under-reporting is probably also confounded by the fact that, although disclosure of this information is requested, there are currently no penalties under the existing World Anti-Doping Code for failing to do so. These findings should prompt a review by antidoping authorities to develop strategies to strengthen the accountability of athletes for declaring this information; potentially through education or disciplinary action.

Potential to enhance performance

The evidence to demonstrate any performance enhancing effects of meldonium in the athlete population is limited. There appears to be some evidence that meldonium may benefit exercise performance in rodents, but specific studies to evaluate potential effects on performance specifically in elite athletes have not been identified. The following studies provide some

further understanding of the actions of the drug that could be linked to effects on performance.

The beneficial effect of meldonium on cerebral circulation disorders and central nervous system functions was demonstrated in a study by Sjakste *et al*.³ patients became more active with decreased motor dysfunction. Meldonium was also reported to be of benefit for the improvement of reduced work capacity and for physical and psychoemotional overexertion.³

A study by Germane⁴ on the effects of meldonium on the behaviour of mice and rats describes increased mobility of the animals, increased exploratory behaviour and enhanced tolerance to prolonged hypoxia after the administration of meldonium. This study also showed a positive effect on the sympathoadrenal system in stressed animals with accumulation of catecholamines in the brain and adrenal glands.

One large randomised, double-blind, placebo-controlled study by Dzerve *et al*⁵ demonstrated that meldonium (1 g/day) in combination with a standard therapy was superior in improving the exercise tolerance of patients with stable angina pectoris compared to treatment with placebo in combination with a standard therapy.

Meldonium is used medically in patients for the treatment of myocardial ischaemia with effects reported to include improved systolic function, inhibited hypertrophy and dilation of the myocardium, improved peripheral blood circulation and increased stress tolerance. Consequently, the use by athletes could potentially result in enhanced personal performance and a shortening of the recovery period after physical activity.

Adverse effects reported by the manufacturers of meldonium include headache, agitation, tachycardia, allergic skin reactions and dyspepsia. Serious adverse effects that pose a significant risk to health or life, after taking meldonium, have not yet been found in the scientific literature. The seemingly safe clinical profile of this substance, coupled with the perception that it may have some effect in enhancing recovery or performance, are all confounding reasons why the drug may be routinely prescribed in young and otherwise healthy athletes.

WADA criteria for banning substances

A substance is considered for inclusion on the Prohibited List if WADA determines that it meets any two of the following three criteria:

1. There is medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or actually enhances sport performance;
2. There is medical or other scientific evidence, pharmacological effect or experience that the use of the substance or method represents an actual or potential health risk to the athlete;
3. That the use of the substance or method violates the spirit of sport.²

Given that the clinical indications for meldonium are for cardioprotective and anti-ischaemic effects, this widespread prevalence of use in an otherwise healthy athlete population is clearly not primarily for a therapeutic reason. Rather, the drug is evidently being used with the intention to either improve recovery or enhance performance—use of a substance with the intention to improve performance is, by WADA's definition, a violation of the spirit of sport.

As shown, there is some pharmacological evidence to suggest that this drug does improve performance, and the widespread use in the athlete community suggests that there is some benefit

being observed that is potentially perpetuating its use among athletes. In addition, the knowledge that 13 competition winners at the Baku 2015 Games, known to have taken meldonium at the time of competition, might also be interpreted as indicating some efficacy of the drug to improve performance, although this cannot be proven through the observations presented in this report. Further research to further explore the potential for performance enhancement in athletes is warranted.

The clinical use of meldonium specifically in young athletes has not been documented, nor is it known what dosages the athletes were taking at the time of competition in Baku. This lack of data raises concerns as to whether the use in this way represents any health risk or longer term clinical consequences in this specific population.

CONCLUSION

The laboratory findings of 66 positive results for meldonium of 762 (8.7%) samples and the active surveillance undertaken by the EOC Medical and Anti-Doping Commission, show the widespread use of this drug by athletes competing at the Baku 2015 European Games. These findings highlight the excessive and inappropriate use and prescribing of this prescription drug in a generally healthy athlete population.

Subsequent to these findings, meldonium has been included as a prohibited substance on the 2016 WADA Prohibited List. The report from the Baku Games would have been a contributing source of surveillance reviewed by WADA in the decision process to determine the status of meldonium. As of 1 January 2016, a Therapeutic Use Exemption (TUE) for its use by a competing athlete must be applied for by the treating doctor, outlining the justification for the clinical use for legitimate medical treatment. This TUE must be approved by the relevant sporting federation or national antidoping organisation prior to the athlete competing. A TUE would not usually be granted if a

What are the findings?

- ▶ There is an alarmingly high prevalence of meldonium use by athletes in sport as demonstrated by the laboratory findings at the Baku 2015 European Games.
- ▶ Thirteen medallists or competition winners were taking meldonium at the time of the Baku 2015 European Games.
- ▶ Meldonium use was detected in athletes competing in 15 of the 21 sports during the Baku 2015 European Games.
- ▶ As of 1 January 2016, the World Anti-Doping Agency has put meldonium on the 2016 List of Prohibited Substances and so it is now banned in sport. Meldonium was not prohibited previously.

How might it impact on clinical practice in the future?

- ▶ Athletes with meldonium found in their system from 1 January 2016 will be subject to disciplinary action and potential sanctions by national and international sporting bodies.
- ▶ From 1 January 2016, a Therapeutic Use Exemption (TUE) must be obtained by the prescriber for an athlete if it is to be given for legitimate therapeutic use.

permitted alternative to the substance exists and can be used instead.

Given the widespread use of this drug in the athlete population, a global awareness campaign for athletes and healthcare providers highlighting that the drug is now prohibited should be undertaken by National Anti-Doping Organisations, to promote awareness and prevent future doping violations as a result of meldonium. In addition, further education for athletes and their medical support personnel about appropriate prescribing of medical drugs only for legitimate medical care is warranted.

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noted in the report and confirmed the permissions of the laboratory to use the data in this way.

Competing interests None declared.

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Provenance and peer review Not commissioned; externally peer reviewed.

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